III. REMARKS

Claims 1-20 are in the case. Claims 1, 3-4, 6-9, 12-15, and 17-18 have been amended; claims 2 and 16 have been cancelled; claims 19 and 20 are newly presented.

Objections

The disclosure is objected to because the specification contains too many grammatical, idiomatic, and spelling errors to list specifically and should be carefully revised. Appropriate correction is required.

Applicant traverses this objection. Although the text is of foreign original and some inconsistencies of grammar may exist, the text is entirely understandable and meets the criteria required by the rules. Withdrawal of this objection is requested.

Claims Rejections - 35 U.S.C. 112, first paragraph

Claims 1-11 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, for the reason that the specification contains subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant traverses this ground for rejection.

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First, applicant identifies in his specification, at page 2 elastase 1 tests known and used in the art at the time of his invention. At page 2, third paragraph applicant identifies a problem with the then existing test, i.e. the traditional elastase-1 ELISA test is not sufficiently sensitive to recognize pancreas elastases.

Inherently then, those skilled in the art did not need to be taught the procedure for determining elastase-1 at the time this invention was made, nor that the detection of elastases had diagnostic significance.

Applicant determined that the elastase protein existed as various iso-enzymes and conceived of a method utilizing the various iso-enzymes to increase the sensitivity of the test. As stated on page 3, lines 17-19,

> "The invention therefore relates to a procedure for producing anti-elastic antibodies in the usual way." [emphasis supplied]

The novelty is specified in the next sentence:

> "... the specific antigens used either single or in combination represent all known elastases iso-enzymes or partial elements of such enzymes or cross-reacting synthetic sequences."

So what is claimed is 1) a method of producing samples containing various elastases, 2) collecting the various iso-forms, 3) raising antibodies to the collected iso-forms and 2) using the set of antibodies so collected in tests thereby

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increasing the sensitivity of the test.

Applicant suggests that each of the steps above comprisies a procedure known in the art and that the statement of the step is sufficient and that once the inventive step of using multiple iso-forms is stated the remaining necessary information is contained in the specification and was known to the art and contained in the references cited hereinbelow.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 and 16 involve method claims and have been amended to recite a positive administration step delimiting how the method is actually practiced.

In claims 1-6, "the serum, secretions, or excretions" are alleged to lack antecedent basis. Applicant believes that antecedent basis exists but for additional clarity applicant has reversed the order of words to obviate this ground for rejection

In claims 2-4, recitations of "the amino-acid sequence" are alleged to lack antecedent basis. Claim 2 has been cancelled and claim 4 amended to obviate this ground for rejection.

In claims 3-4, improper Markush language is used to claim the members of the group. The claim has been amended to obviate this ground for rejection.

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Claim 4 fails to end with a period. It is believed that --antigens-- rather than "antigenes" was intended at line 2. At line 3, --immunization-- rather than "the antigens" should be inserted. Applicant thanks the examiner for his suggestion and has amended the claim to obviate these grounds for rejection.

In claim 5, "the antibodies" is alleged to lack antecedent basis. Claim 1 from which claim 5 depends has been amended to provide antecedent basis for the use of the term in claim 5.

Claim 6 is alleged to be of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 6 has been amended to independent form to obviate this ground for rejection.

In claim 7 and claims dependent thereupon, the term "standard" has been deleted and the correct sequence identifiers supplied thus obviating these grounds for rejection.

In claim 8, the term "suitable" has been deleted thus obviating this ground for rejection.

The examiner states that claims 10, 11, and 16 are of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 10 and 11 each relate to single type of antibody whereas claim 7 from which they depend relates to both types of antibodies. Thus, the dependent claims do further limit claim 7.

Claim 16 has been cancelled.

In claims 12-15, applicant has amended the claims to provide correct sequence identifiers.

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Claims 17 and 18 are rejected as indefinite in that the claims set forth an intended use but fail to point out what components are included or excluded by the claim language in that "the diagnosis" lacks antecedent basis.

The examiner appears to be objecting to the definite article "the". Applicant has amended claim 17 to delete the article "the" thereby obviating this ground for rejection.

Claim Rejections - 35 U.S.C. § 102(b)

Claims 1-8 and 10-18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Scheefers et al. (USP 5,622,837) in light of the instant disclosure for reasons of record.

Claims 1-8, 10, and 12-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sziegoleit et al. (Clin. Biochem. 22: 79, 1989) in light of the instant disclosure for reasons of record.

Applicant traverses these grounds for rejection.

The examiner states that, notwithstanding applicant's assertions to the contrary, Scheefers et al. clearly teach elicitation of both polyclonal and monoclonal antibodies to purified enzyme, not only to the peptide disclosed in the reference. And, as is noted by applicant, the excluded sequence is not found in the purified enzyme.

The examiner argues that the enzyme isolated from multiple organs by the references of Sziegoleit et al. or Scheefers et al. would inherently be a mixture of the elastase I isoforms (i.e. elastases IIIA and IIIB), and polyclonal antibodies elicited thereto would inherently bind to the isoforms and cross-

react with similar epitopes as found in elastase II.

The examiner correctly points out that the Patent and Trademark Office does not have the facilities and resources to provide the *factual* evidence needed in order to establish that there is a difference, in the first place, between the reagents of the prior art and those instantly disclosed and, that if there is such a difference, that such a difference would have been considered unexpected by one of ordinary skill in the art.

The examiner states that the burden is upon applicant to present such factual evidence.

In response, applicant is providing a number of abstracts along with this response elucidating the differences between the cited references to Scheefers et al. and Sziegoleit et al. and the instant application.

Since all of the experiments presented in the abstracts have been performed using the claimed procedure, the practicability and suitability of the invention and the distinction over the prior art is clearly shown by the 10 publications.

Summarizing several of the abstracts, the inventive method has been proven extremely useful for

- the detection and diagnosis of chronic pancreatitis (Keim et al., 2000, found on page 2 of the list), also in the routine laboratory (Esposito et al., page 4)

- determining pancreatic insufficiencies in children (Tomasova et al., 2003, page 3-4)

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- assessing the exocrine pancreas function in patients suffering from Cystic Fibrosis (Tomasova et al., 2002, page 4, last two sentences of the abstract) .

Furthermore Weiss et al., 2006, (page 1) exemplarily investigate three inventive antibodies and describe them as specifically binding all elastase isoforms present in human pancreatic juice (elastases 3A and 3B), as evidenced by mass spectrometry.

The list also comprises several abstracts directly comparing the inventive procedure to the detection system according to Scheefers et al. (USP 5,622,837), which is distributed by the company ScheBo(the assignee of USP 5,622,837):

Hahn et al., 2005, (page 1) describe a higher specificity of the inventive test for clinical detection of chronic pancreatitis, in comparison with the monoclonal test of competition.

Mienje et al., 2004, (page 2, last sentence of the abstract) describe a higher specificity and reproducibility of the inventive test kit, which is distributed by the Applicant, for the diagnosis of pancreatic insufficiencies in patients suffering from Cystic Fibrosis, in comparison with the ScheBo kit.

Keim et al., 2002, (pages 2-3) show a superior specificity of an ELISA according to the invention for detecting chronic pancreatitis in comparison with the tests of competition (ScheBo and chymotrypsin test).

Keim et al., 2000 (page 3) show a better specificity and accuracy of the inventive test for diagnosis of chronic

pancreatitis in comparison to the competing test (ScheBo), whereby the inventive test was also more specific, when healthy individuals and blood donors were tested.

Hahn et al., 2001, (page 4) studying the frequency of exocrine pancreatic insufficiency in Diabetes mellitus, report that the ScheBo assay finds many more ostensibly insufficient patients than the inventive assay, probably due to the lack of diagnostic specificity of the ScheBo assay.

These references provide clear evidence that the inventive procedure is clearly superior to the test systems according to Sziegoleit et al. and Scheefers, Scheefers-Borchel and Sziegoleit, USP 5,622,837.

As the results are different, it is clear that there is a difference between the reagents of the prior art and applicant's reagents and that the argument of inherency is not valid. Thus, the prima facie case has been overcome and applicant has met its burden.

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Favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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Synopsis of publications concerning the Pancreatic Elastase Test according to U.S. Serial Number 09/786,725 (Applicant: Bioserv)

Assessment of isoform specificity of a polyclonal Elastase ELISA

F U Weiss1, M Ruthenbürger1, E Hammer2, U Völker2, M M Lerch1. Published in: Journal of Pediatric Gastroenterology and Nutrition 43:E32 # 58, 2006

1 Department of Gastroenterology, Endocrinology and Nutrition, Ernst-Moritz-Arndt-University Greifswald, Germany, and 2Laboratory for Functional Genomics, University of Greifswald, Germany

Introduction: Elastase is secreted from the pancreas and passes through the GI-tract without significant degradation. Exocrine pancreatic function analysis can therefore be performed with Elastase stool tests. Five different isoforms of human pancreatic elastase (PA I, IIA, IIB, IIIA, IIIB) have been identified. Three different polyclonal antisera that are used in a commercial ELISA were investigated for their specific recognition of human elastase isoforms in human pancreatic juice.

Material and Methods: Secreted proteins from human pancreatic juice were analysed by one or two-dimensional gel-electrophoresis, followed by westernblot analysis using 3 different polyclonal anti-Elastase antibodies (BIOSERV GmbH, Germany) and MALDI-TOF-MS. Elastase-activity was analysed in immunoprecipitates from human pancreatic juice using a fluorogenic Elastase substrate. Finally, cross-reactivity of the antibodies was tested against pancreatin from pig pancreas.

Results: In 1D Western blots of pancreatic juice all three polyclonal antisera against human Elastase detected a single ~30kDa protein. Immunoprecipitates with these antibodies exhibited elastase activity as determined with the fluorogenic Elastase substrate. In 2D-Westernblots (pH3-10) proteins in the molecular weight range of ~30 kDa were separated into a number of spots of different isoelectric points (pI). MALDI-TOF-MS-Analysis of these spots revealed the presence of pancreatic Elastase IIIA and IIIB isoforms, but not Elastase II or Elastase I isoforms. Western blot analysis of pancreatin from pig pancreas revealed no cross-reactivity with any of the three antisera tested.

Conclusion: All three commercial antibodies that are used in a polyclonal Elastase ELISA preferentially detect human Elastase isoforms IIIA and IIIB, and do not cross-react with pig pancreatin. At present differences concerning expression and specific function of PA II or PA III isoforms are still unknown, but we could demonstrate, that PA III isoforms clearly possess Elastase activity as determined by a fluorogenic Elastase substrate. Elastase I is not an enzyme expressed in the adult human pancreas and should therefore not be referred to in commercial test kits for exocrine pancreatic function.

A New Fecal Elastase 1 Test Using Polyclonal Antibodies for the Detection of Exocrine Pancreatic Insufficiency

Jan-Uwe Hahn, Sabine Bochnig, Wolfgang Kerner, Helma Koenig, Birgit Sporleder, Paul Georg Lankisch, Patrick Maisonneuve, Albert B Lowenfels

Published in: Pancreas, Vol. 30, No. 2, March 2005, pp. 189 – 190

Summary: The fecal elastase 1 test from BIOSERV Diagnostics was compared with the test of the competition, with the secretin-cerulein test as direct pancreatic function test (gold standard) and with the quantitative fecal fat analysis. 31 patients sent to the Department of Medicine at the Municipal

BIOSERV Diagnostics GmbH, Dr.-Lorenz-Weg 1, 18059 Rostock, GERMANY, www.bioserv-diagnostics.com

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Hospital in Lueneburg ... suspected chronic pancreatitis were inve ...ed. Exocrine pancreatic insufficiency was classified as mild, moderate or severe.

According to the results of the SCT, 11 of the 31 patients had exocrine pancreatic insufficiency that was due to chronic pancreatitis.

The **sensitivity** in detecting exocrine pancreatic insufficiency was 64% for both test procedures. The **specificity** of the new test was **much higher** than that of the older one (95% vs. 80%). When patients with severe exocrine pancreatic insufficiency were evaluated, the sensitivity of both tests was 83% and thus similar to those rates shown in previous studies for the monoclonal test.

Conclusion: .. the polyclonal test seems to have the same sensitivity as the monoclonal test but offers a **higher specificity**. Therefore, it is **more useful** for differentiating between pancreatic and nonpancreatic steatorrhea, which is a frequent clinical problem.

Polyclonal versus Monoclonal ELISA for the Determination of Fecal Elastase 1: Diagnostic Value in Cystic Fibrosis and Chronic Pancreatic Insufficiency.

Yvette Miendje, Diane Maisin, Marie J. Sipewa, Pierre Deprez, Jean P. Buts., Philippe De Nayer, Marianne Philippe

Published in: Clinical Laboratory, Vol. 50, No. 7+8, 2004; pp. 419 - 424

Summary: The authors collected single spot samples from two groups of patients. The group of adults included 13 healthy subjects (HS), 12 patients with non-pancreatic gastrointestinal disease (NPGD), 26 with chronic pancreatitis with presence of calcification (CCP) and 14 without calcification (NCP). The group of children included 17 cases of cystic fibrosis (CF) and 21 controls (CO). After a common extraction, both assays were performed as recommended by the manufacturers.

In the children group, Sensitivity was 94% for both assays. Specificity was 100% for the BIOSERV kit and 95% for the Schebo kit. For the adult group, Sensitivity was 82% for the BIOSERV kit and 80% for the Schebo kit. The specificity was 92% for both assays.
The interassay CVs computed from 12 consecutive assays of three different fecal samples (low, medium and high value) were 2.7 to 5.1% (mean 3.6%) and 3.7 to 5.9% (mean 5%) for Bioserv and ScheBo, respectively.

Both the kit from BIOSERV Diagnostics and the Schebo kit were found suitable for the detection of severe pancreatic insufficiency either in adult patients or in children. However, the specificity and the reproducibility of the BIOSERV Diagnostics kit was slightly better.

Clinical Value of a New Fecal Elastase Test for Detection of Chronic Pancreatitis

Volker Keim, Niels Teich, and Joachim Moessner

Published in: Clinical Laboratory, Vol. 49, No. 5+6, 2003; pp. 209 – 215

Summary: Fecal samples from 212 patients were taken. Chronic pancreatitis was assumed when ductal alterations were present in ERCP. The severity of disease was assessed according to the Cambridge classification. Elastase (test from ScheBo, Germany) and chymotrypsin (Roche Diagnostics) were measured. As a new parameter an Elastase ELISA from BIOSERV (Rostock, Germany) was employed. Specificity, sensitivity, and accuracy of each test as well as the ROC curves were calculated.

In 45 patients (21.2%) chronic pancreatitis was diagnosed.

BIOSERV Diagnostics GmbH, Dr.-Lorenz-Weg 1, 18059 Rostock, GERMANY, www.bioserv-diagnostics.com

Sensitivities:

BIOSERV:	77,8%
Schebo:	68,9%
Chymotrypsin:	57,8%

Specificities:

BIOSERV:	76,0%
Schebo:	77,2%
Chymotrypsin:	52,7%

Conclusion: "The new elastase assay could probably replace the older test and was also much better than chymotrypsin."

Value of polyclonal Elastase ELISA for diagnosis of chronic pancreatitis

V. Keim, N. Teich, and J. Mössner.

Abstract published in: Pancreas, Volume 21, Number 4, page 453, November 2000

Summary: BIOSERV superior to Schebo and to Chymotrypsin: Bioserv diagnostic specificity 12% better than Schebotech, accuracy 10% better, diagnostic sensitivity 2% better "... the newly available polyclonal pancreatic elastase assay was superior both to the monoclonal Elisa and to chymotrypsin."

	Fecal Elastase 1 (BIOSERV)	Fecal Elastase 1 (ScheboTech)	Cymotrypsin (Roche Diagnostics)	Patient Types
Sensitivity	50%	48%	44%	64 patients diagnosed with chronic pancreatitis out of 699 abdominal diseases
Specificity	75%	63%	55%	
Accuracy	72%	62%	54%	
Specificity	92%	86%		Healthy individuals (n=40) and blood donors (n=78)

Quantification of fecal Elastase-1 using either polyclonal or monoclonal antibodies.

Carlos A Garcia-Bueno, Thomas M (Michael) Rossi , Kusuma W Lee, Melawati T Yuwono, Mary Bridge, Amy Robinson, Amin Tjota

Abstract published in: Gastroenterology, vol 122, no 4 page A-510, April, 2002; Poster T1713 "The polyclonal antibody based method for detection of fecal E-1 is as sensitive as the monoclonal test system."

Summary: Comparison of BIOSERV and Schebo to the **secretin-pancreozymin test (gold standard).**
BIOSERV at least as good as Schebo, both comparably to the gold standard.

Proper interpretation of Elastase-1 activities in Stool: experience of the Prague CF centre

Helena Tomášová, Dana Zemková, J. Bartosova, V. Skalicka, Stanislava Kolouśková, Jiri Nevoral, Milan Macek Jr., Vera Vávrová

Poster 237 at the 25th Congress of the European Cystic Fibrosis Society, Genova, Italy, 20-23 June 2002

Published in:

BIOSERV Diagnostics GmbH, Dr.-Lorenz-Weg 1 18059 Rostock, GERMANY, www.bioserv-diagnostics.com

- (Abstract) . ıal of Cystic Fibrosis, the Official Journ. the European Cystic Fibrosis Society, Volume 1, Supplement 1, page 138, ISSN 1569-1993
- (Article) Proceedings of the 25th European Cystic Fibrosis Conference (Volume ISBN 88-323-2622-1, CD ISBN 88-323-2623-X); page 111 – 114

Also available: complete original poster (directly generated pdf)

Summary: Use of BIOSERV Elastase-1 ELISA in research and routine.
Elastase-1 examination represents a noninvasive, relatively simple method, assessing the exocrine pancreatic function. In patients suffering from Cystic Fibrosis the exocrine pancreatic function is severely impaired, whereas the impairment in patients suffering from Diabetes mellitus type 1 seems to be less grave than in Cystic Fibrosis.

Experiences with fecal Elastase-1 determination in children with and without pancreatic insufficiency

Helena Tomášová, Vera Vávrová, Dana Zemková, Jiri Nevoral, Stanislava Kolouśková, B Kocmichová, Milan Macek Jr.

Poster 112 at the Meeting of the Czech and Slovak Physiological Societies, Plzen, February 7th, 2003

Summary: Fecal elastase examination represents a non-invasive, simple method for assessing the exocrine pancreatic function.
Whereas in 124 controls without pancreatic or intestinal disorders the secretion of E1 was normal, it was significantly decreased in IDDM patients and very much decreased in CF patients. Correlation with sweat Cl⁻ and with the CFTR genotype in CF patients was highly significant. E1 determination seems to be more sensitive than other indirect tests like chymotrypsin and does not require the interruption of an enzyme substitution therapy.

The Frequency of exocrine pancreatic insufficiency in Diabetes mellitus type 1 – also a methodical problem?

Hahn, J.-U., Wadowska, K., Heinke, P., Peters, H., Rjasanowski, I., Kerner, W.

Poster 20-04 at the 36th Annual Meeting of the German Diabetes Society

Published in: Diabetes und Stoffwechsel, 10, Suppl. 1 (2001)
Summary: Schebo finds many more ostensibly pancreatically insufficient patients than BIOSERV, probably due to the lack of diagnostic specificity of the Schebo assay. More soon to come.

Elastasi fecale e pancreatite cronica

Esposito C., Formicola V., Spanò A., Spina M.

Use of the BIOSERV Elastase-1 in the routine laboratory.
"Attualmente la determinazione dell'elastasi fecale con metodica Elisa è un presidio di prima scelta nella diagnostica dell'insufficienza esocrina del pancreas. E' un test di **facile e rapida esecuzione** per il laboratorista con il **vantaggio di non essere invasivo** per il paziente."

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